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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _30 November 2007_.
2a)☒ This action is **FINAL**.   2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _49,50,52,53 and 56-77_ is/are pending in the application.
    4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) _49,50,52,53 and 56-77_ is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
    a)☐ All   b)☐ Some * c)☐ None of:
        1.☐ Certified copies of the priority documents have been received.
        2.☐ Certified copies of the priority documents have been received in Application No. _____.
        3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO/SB/08)
    Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413)
    Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

DETAILED ACTION

1.   This office action is written in response to the papers received 11/30/07.   Any rejections

which are withdrawn but not addressed have been overcome by amendment to the claims or

cancellation of the rejected claims. This action is FINAL.

Claim Rejections - 35 USC § 112

2.   Claims 50, 52, 53, 56, 57, 58, 70, 72,76, and 77 are rejected under 35 U.S.C. 112, first

paragraph, as failing to comply with the written description requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. This is a rejection for new matter.

3.   In claims 50, 70 and 72, the limitation that the blood samples "comprises leukocytes

which a have not been fractionated into cell types" is new matter.   Such a recitation includes, for

example, testing a blood sample where the red blood cells and the white blood cells have been

separated, and also includes, the testing of whole blood RNA. There is clearly basis for the

latter, but not the former.

4.   Applicant asserts in the remarks that this claim limitation finds clear support in the

specification, including figure 5C which shows standardized fractions of leukocytes. However,

these are not leukocytes that have not been fractionated into cell types, as they have clearly been

fractionated into cell types. While RNA levels have been determined in each of the fractions,

this is not basis for the negative limitation "have not been fractionated into cell types." There is

no discussion or example in the specification of the testing of RNA in blood samples which

comprise leukocytes which have not been fractionated into cell types. Applicant has attempted

to present a claim which excludes a particular process step from a method (that is, fractionating

the leukocytes) and then provides basis for the exclusion of the step in a method where the

opposite occurred. This is not sufficient basis for the claim limitation because there is nothing in

the specification that suggests applicant contemplated the exclusion of a step of fractionating

leukocytes into cell types. Therefore, claims 50, 70, and 72, as well as all claims which depend

from these claims are rejected for having new matter.

4.   Claims 76 and 77 are further rejected as having new matter because they introduce a

negative proviso into the claims (i.e. "none of said control subjects is selected from the group

consisting of subjects…") which does not appear to have basis in the specification as originally

filed.

5.   Claims 49, 50, 52-53, and 56-77 are rejected under 35 U.S.C. 112, first paragraph, as

failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

        The invention of claim 49 is expressly drawn to a method detecting osteoarthritis in a

human test subject. The claims all include a step of quantifying a level or RNA encoded by a

desmuslin (DMN) gene in a blood sample obtained from said human and comparing the level

with a quantified level of RNA encoded by said gene in blood samples of control subjects which

are classified as healthy control subjects, also comparing the test level with a quantified level of

control RNA encoded by said gene in blood samples of control subjects which are classified as

having osteoarthritis and wherein said comparison of a statistically significant determination resulting from steps the comparisons that expression of said gene in said sample of said test subject is different relative to said samples of said control subjects classified as healthy control subjects, and is similar relative to said samples of said control subjects classified as having osteoarthritis is indicative of osteoarthritis in said human test subject.

Claim 59 is drawn to a method for detecting expression of a gene encoding a Desmuslin (DMN) in a human "test subject." Claims which depend from claim 58 set forth that the detected expression is quantified and compared to quantified level of control RNA encoded by said gene in blood samples of control subjects. Listed control subjects include healthy subjects and subjects that do not have osteoarthritis. Further dependent claims set forth steps of classifying or identifying the test subject as being a candidate for having osteoarthritis depending on the outcome of the comparing steps. Thus, it is clear that the intended use of claim 58 and those that depend from claim 59 is for classifying or identifying the test subject as being a candidate for having osteoarthritis.

Claim 68 is drawn to a method of screening a human test subject "for being a candidate for having osteoarthritis" and includes similar steps of detection of the DMN gene in a blood sample, quantifying the expression and comparing the level to a quantified level of control RNA encoded by said gene in blood samples of control subjects classified as healthy subjects, where said test subject is a candidate for OA if said level of RNA encoded by said gene in said blood of said human is significantly different relative to that of said control subjects classified as healthy subjects with a p value of less than 0.05.

In claim 71, the invention is drawn to a method a method for classifying DMN gene expression in a human, and sets forth steps of quantifying a level of RNA encoded by a DMN gene in a test subject, comparing that level to a level of RNA found in blood samples from control subjects having osteoarthritis and also comparing it to control subjects who are healthy. The independent claim states that based on particular determinations, the classification of DMN gene expression results either with that of said subjects having osteoarthritis or with that of subjects who are healthy.

The nature of the invention requires the knowledge of a reliable relationship between DMN expression in blood and the presence of or indication of osteoarthritis. Further, the practice of the invention requires an understanding of how the presence of osteoarthritis effects the level of DMN expression in human blood. The practice of the invention requires an understanding of how the presence of osteoarthritis effects the level of DMN expression in human blood in patients having osteoarthritis versus patients that do not have osteoarthritis but may have some other disorders. The nature of the invention requires the knowledge of a reliable association between DMN expression and the ability to classify a particular individual's expression with the expression of subjects having osteoarthritis or not having osteoarthritis, and further, the use of this method requires that there is an underlying assumption that this classification is meaningful. Reading the claims in light of the specification it is clear that applicant intends to use such a classification method in order to provide a tool that is used as part of a diagnostic process, and such a use requires the knowledge of a reliable association underlying the classification. Many of the claims additionally require a step of comparing the level of RNA detected in a test subject to "a quantified level of control RNA encoded by said

gene in blood samples of control subjects." To practice these claims, it is essential to know the quantified level of control RNA encoded by said gene in blood samples of control subjects.

Scope of the claims

Many aspects of the claims remain quite broad.

In some claims the health status of the control individuals is entirely undefined, and encompass subjects with osteoarthritis, cancer, healthy patients, patients with some other disease, such as patients with a particular stage of osteoarthritis, patients with osteoarthritis in combination with other conditions, or patients with renal cell carcinoma etc. Claims which recite that the control subjects "do not have osteoarthritis" remain quite broad given that this could encompass control subjects with any other possible disease, disorder or treatments.

The claims are very broad in scope because they encompass that ANY level and direction of difference in gene expression between the healthy controls or the controls not having osteoarthritis is indicative of said osteoarthritis, if that difference is "statistically significant." That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims. Most claims do not recite a level of statistical significance that is required to be reached, and so, the claims remain quite broad since no particular level is required, and the claims even encompass using different levels of statistical significance for different comparisons. The phrase "statistically significant" describes a mathematical measure of difference between groups, not a particular level of difference which is acceptable. There is no universally accepted level of "statistically significant."

Teachings in the Specification/Examples

Regarding osteoarthritis, the specification provides example 24 wherein gene expression profiles of blood samples from individuals having osteoarthritis were compared with normal individuals, that is healthy patients. The specification teaches that 300 genes were identified as being differentially expressed, and regarding the instant claims, table 3O provides a list of these genes (Example 24). DMN is among the genes.

The tables list genes that were differentially expressed, but does not provide any further information. For example, the tables do not teach if the expression was higher or lower in osteoarthritis patients versus controls. The specification is silent as to any "quantified level of control RNA encoded by said gene in blood samples of control subjects."

The specification does not provide any guidance as to the level of "difference" that is sufficient (1 fold, 2 fold, etc) to result in a conclusion that osteoarthritis is detected, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples.

Additionally, DMN is not reported as being differentially expressed when tests are done with patients having osteoarthritis and hypertension as compared with normal patients (Table 3A), or osteoarthritis and obesity as compared with normal patients (Table 3B) or osteoarthritis and allergies as compared with normal patients (Table 3C), or osteoarthritis and subject to systemic steroids compared with normal patients (Table 3D). Furthermore, the gene does not appear in Table 3AB which provides genes that are differentially expressed in blood from patients with mild or severe OA but genes relevant to asthma, obesity, hypertension, systemic steroids and allergies have been removed. Thus, the gene is not significantly differentially expressed in all patients with osteoarthritis relative to healthy patients.

The specification fails to provide information about an essential aspect of the invention, namely, the nature of the difference in expression that was observed between osteoarthritis patients and healthy patients. Furthermore, though the specification teaches that this gene is differentially expressed in osteoarthritis patients versus healthy patients, the specification teaches this is true for hundreds of genes. There is no guidance or analysis of data in the specification to suggest that this gene in particular is sufficient to conclude that osteoarthritis is present in a sample, as is instantly claimed. This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

State of the Prior Art and Level of Unpredictability

The expression of genes in example 24 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Observing differences in expression between two populations is a highly unpredictable endeavor. The specification clearly exemplifies this for the case of DMN. The specification

teaches differential expression of this gene between populations of patients with osteoarthritis

and healthy controls. The art of Twine et al. teach that DMN is differentially expressed in the

blood of patients who have renal cell carcinoma versus healthy controls (Table 4, ¶0307, and

Example 4). So first, even if one carried out the claimed analysis on a test subject, and if one

observed a level of expression, it is highly unpredictable how would one begin to know if that

level of expression indicated osteoarthritis, renal cell carcinoma, both, one but not the other,

something in between or even some other condition or disorder for which the expression profile

has not yet been determined.

Further, DMN it is not listed in the tables for differentially expressed genes in patients

who have both osteoarthritis and other diseases or conditions versus normal controls. So, this

exemplifies that a particular gene is not always differentially expressed in populations of patients

having osteoarthritis versus healthy controls. Observing the differential expression result is

population dependent- something about patients with osteoarthritis and other diseases or

conditions changes the observation. It is unknown and unpredictable whether this is also true for

differential expression observations in other diseases. Furthermore, although DMN was not

observed to be differentially expressed in any of the other examples in this specification, it is

unknown and unpredictable whether it would be expressed in the blood of patients having other

bone related diseases or other types of arthritis or any other diseases which were not tested in the

instant specification or diseases which were tested in the instant specification but in a different

population of test subjects, and whether this expression would be different from levels of

expression in healthy controls. A method for detection which relies on a comparison between

expression in the blood of a test subject and control subjects requires the knowledge of this

information in order to reliably "detect" osteoarthritis in a human test subject, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is indicative of osteoarthritis, yet the claims are sufficiently broad so as to imply this is the case. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. But even if one were to obtain the same result, it would be unknown because applicant did not disclose the magnitude of difference in expression between osteoarthritis patients or controls, nor did applicant disclose the direction of variation. All of these inquiries are particularly important in this case since the specification is silent as to which differential expression observations would be sufficient to detect the presence of osteoarthritis.

Further, the claims of the instant application set forth the comparison of the gene expression in a single individual versus as few as two other individuals, and they set forth that a comparing gene expression between the two is "indicative of" osteoarthritis. Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control expression of DMN in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control group is "indicative of" any of the recited osteoarthritis. Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates)

(p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35

individuals varied by a factor of 17; and that in expression of the 40 genes with the highest

variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is

thus unpredictable as to whether or not any level of altered gene expression is indicative of a

osteoarthritis or the absence of osteoarthritis cancer.

The unpredictability of correlating gene expression level to any phenotypic quality is

taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as

microarray data, must be interpreted in the context of other biological knowledge, involving

various types of 'post genomics' informatics, including gene networks, gene pathways, and gene

ontologies (p.53, left col.). The reference indicates that many factors may be influential to the

outcome of data analysis, and teaches that expression data can be interpreted in many ways. The

conclusions that can be drawn from a given set of data depend heavily on the particular choice of

data analysis. Much of the data analysis depends on such low-level considerations as

normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton

et al (2001) further teaches the difficulty in applying gene expression results. Newton et al.

teaches that a basic statistical problem is determining when the measured differential expression

is likely to reflect a real biological shift in gene expression, and replication of data is critical to

validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single

embodiment within the claimed invention. In particular, the specification does not provide

adequate guidance to appraise one of ordinary skill in the art as to what levels of DMN gene

expression must be observed to successfully conclude that osteoarthritis is present. Further, although the specification teaches there are differences in DMN levels in a osteoarthritis population versus a control patient population, the specification is silent as to the nature of the "difference" in magnitude or direction. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would begin by trying to reproduce the results observed in the instant specification to determine if there is a relative upregulation or downregulation of DMN in osteoarthritis patients versus healthy control patients, as the specification does not even provide this minimal guidance. Without this knowledge one would not even begin to know how to interpret any results obtained in practicing the claimed methods. For example, consider the comparison of a test result and a control population of healthy individuals. How different from the average level of expression of healthy individuals would the test result have to be to indicate osteoarthritis? Would any difference, up or down regulation be indicative of osteoarthritis? Or could one indicate osteoarthritis and one renal cell carcinoma or some other disease? Is DMN expressed in the blood of individuals with a disease other than renal cell carcinoma and osteoarthritis? Is this expression also diagnostic of other degenerative diseases or other diseases of the joints or other disorders entirely unrelated to osteoarthritis? What populations could be tested and expected to provide a reliable result? For example, if a subject has allergies, would the practice of the claimed assay be reliably informative in the event that DMN expression is different or the same as the control subjects? In

order to reliably use a method for detecting osteoarthritis, one would first have to answer at least

these questions. One would also, however, have to carry out this testing for validation, for it is

possible that the result observed in the instant specification is intrinsic to the cohort of patients

evaluated in applicant's study. Further, one would have to undertake experimentation to

determine difference thresholds required to determine that a patient has or does not have a

disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of

DMN in a test subject and comparing this expression to control subjects, wherein the comparison

itself "is indicative of osteoarthritis." The identification of gene differential expression/disease

indication relationships is a highly unpredictable endeavor, requiring extensive experimentation.

The specification provides minimal guidance. In light of the factors discussed, therefore, it is

concluded that it would require undue experimentation to practice the claimed invention.

Although some of claims are drawn to a method of "detecting expression" or "classifying

expression," and not to diagnosis or identifying increased likelihood of disease or the like, it is

critical to understand how the classification can be used in order use the claimed invention. In

this case, the specification does not provide sufficient guidance as to how to use the detecting or

classification methods other than in methods that are directed towards diagnostic purposes.

What is the meaning of classifying expression "with that of subjects having" osteoarthritis cancer

or with subjects who are healthy? While one could do the method steps as written, thus

satisfying the "how to make" aspect of 112 1st paragraph, the specification does not provide

sufficient disclosure to satisfy the how to use aspect of the requirement.

The data in the specification is not replicated. As discussed in the rejection, it is

established that the technology on which the instant claims is based is a highly unpredictable

technology, and in the face of such a high level of unpredictability, replication is necessary

before results can be considered sufficient to support claims directed at classifying the gene

expression of an individual test subject.   Therefore, even this claim, after having considered all

of the factors set forth in this rejection, lacks proper enablement.

Claim Rejections - 35 USC § 102

6.   The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7.   Claims 59, 61, 62, 63, 64, 65, 70, 72, 73, and 77 are rejected under 35 U.S.C. 102(a) and

102(b)as being anticipated by William Chittenden, dissertation submitted to the faculty of

Virginia Polytechnic Institute and State University, August 2002.

8.   These claims are not fully supported under 112 1st paragraph in the instant application nor

any of the previously filed applications for at least the reasons discussed in this office action.

This reference is applied under 102(a) and 102(b). If applicant establishes support for the

claimed invention to a prior application such that the 102(a) and/or 102(b) does not apply the

rejection will be withdrawn.

Chittenden teaches quantification and analysis of gene expression in mRNA isolated

from whole blood, by isolating cells, precipitating RNA, producing cRNA and hybridization

with the probe array HG-U133A, quantification of hybridization and calculation of differential

expression. It is an inherent property of this array that it contains probes to DMN, and thus, the

method taught by Chittenden is a method which uses an oligonucleotides of predetermined

sequence which are specific for DMN. This chip also inherently has thereupon housekeeping

genes that are used for quantifying expression.   Further Chittenden tests individuals with disease

and healthy controls (p. 58-59, 62-66). Chittenden does not specifically discuss DMN

expression, but it would have inherently been detected in the blood of healthy controls by the

hybridization and array reading methods.

Claim Rejections - 35 USC § 103

9.   The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in
> section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are
> such that the subject matter as a whole would have been obvious at the time the invention was made to a person
> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the
> manner in which the invention was made.

10.   Claims 59, 61-65, 70, 71, 72, 73, 74, 75 and 77 are rejected under 35 U.S.C. 103(a) as

being unpatentable over Carman et al. (US 2003/0170743) in view of Sharma et al. (WO

98/49342).

Carman et al. teach a method for detecting expression of DMN gene in a human test

subject comprising detecting RNA encoded by said gene in said subject using an oligonucleotide

of predetermined sequence which is specific for RNA encoded by said gene and/or for cDNA

complementary to RNA encoded by said gene.

In particular Carman et al. teach using DNA chip expression analysis using the U95v2 A, B, and C chips provided by Affymetrix. This collection of chips inherently has thereupon probes for the analysis of DMN expression, and by using this chip they inherently tested for and detected any expression of this gene. This chip also inherently has thereupon housekeeping genes that are used for quantifying expression. In this rejection the test subjects suspected of having osteoarthritis are those who are disclosed as having osteoarthritis. Expression that was at least three fold different was classified as differently expressed thus, the test subjects' expression was classified as that of a person having schizophrenia versus healthy controls when there was a two fold difference (p. 6) and if the p value was <0.001 (p. 6).

Carman et al. do not teach detecting applying their analysis to the gene expression in a blood sample, and in particular detecting DMN in a blood sample.

Sharma et al. teach that from the very early stages of diseases the whole organism response to the changed condition (p. 10, 4th full ¶). In light of this, Sharma et al. teach a method for identifying a marker useful for diagnosing a disease comprising the steps of detecting the presence of RNA in an unfractionated sample of whole blood from each of one or more subjects having said disease and quantifying a level of said RNA in said sample. Namely, Sharma et al. teach the preparation of gene transcript patterns beginning with extraction of mRNA from tissues, cells or body parts of an individual or organism which has a disease or condition (p. 7, final ¶, p. 12, 1st ¶), and particularly teach the isolation of mRNA from unfractionated whole blood samples, where unfractionated is interpreted as meaning that the cell types within blood were not separated from one another (p. 35, section 5.1.1). Sharma et al. teach quantifying the level of expression and determining a difference between the quantified

level in the sample from the diseased subject and a similarly quantified level of genes of control

RNA from an unfractionated sample of whole blood from each of one or more first control

subjects (p. 5, step (d); p. 15, first full ¶; p. 18, step (f); p. 11, final ¶). Sharma et al. teach that

these methods are carried out by producing amplification products from RNA extracted from an

unfractionated sample of whole blood (p. 18 and p. 35, Example 5). Sharma et al. specifically

suggest that this method can be applied to the study of schizophrenia (p 6, 3rd ¶).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the

time the invention was made to have modified the methods taught by Carman et al. so as to have

additionally tested the blood of the patients having osteoarthritis and the healthy control samples.

One would have been so motivated by the express teachings of Sharma et al. that disease exerts a

global effect on individuals and that this effect can be measured by gene expression in the blood.

The identification of markers for disease in the blood suggests a potential minimally invasive

method to detect this disorder. One would have been motivated to continue to use the

microarray analysis taught by Carman et al. since the use of the microarray enables large scale

screening of many different human genes, and Sharma et al. expressly teach that marker genes

may be identified by differential hybridization methods, which Carman use (see Sharma,

paragraph bridging pages 4-5).

Response to Remarks

Applicant traverses the rejection for lack of enablement. The claims were extensively

amended, and the rejection has been amended to address the amended and newly filed claims.

The remarks are addressed insofar as they remain relevant.

Applicant states on page 11 that the instant claims recite two clearly defined sets of

controls; patients having OA and healthy controls. However, many of the claims are broader,

with some not defining the controls and with some including any controls that "do not have

osteoarthritis."

Applicant states that the elected biomarker DMN is enabled as an indicator of OA as

described in the claims without disclosing the direction or level of difference that exists between

patients having OA and individuals not having OA (p. 12). Applicant argues that the fact that

the claims require determination of a statistically significant similarity between the test subject

and control subjects having OA disease makes it unnecessary to include the direction and

magnitude of the difference because no direction or magnitude information is required in order to

compare for similarity, stating that the declaration exemplifies that it would not take undue

experimentation to make the claimed comparisons. Applicants contend that it does not require

undue experimentation for one of skill in to determine the inherent direction or level of the

statistically significant differential expression required for the claimed methods of detecting a

osteoarthritis, given the widely established and validated analytical tools for analyzing gene

expression, and so it is not necessary for applicant to have taught the exact direction or level of

difference between the two populations for one of skill to practice the invention (p. 12).However,

the rejection is maintained, even in light of the declaration due to the highly unpredictable nature

of this technology, as discussed in the rejection. The instant specification fails to provide a

critical piece of information with regard to understanding the relationship between DMN

expression and OA. The specification invites one of skill in the art to undertake experimentation

to (a) determine the relationship between OA and DMN expression and then to validate that

relationship. There is a fundamental absence of information given in the specification. The claims all set forth comparing the test level to "a quantified level of RNA encoded by said gene in blood samples from control subjects…" but the specification does not provide this quantified level, or any quantified level. So, it is left to one of skill in the art to establish what is critical for the practice of the invention. While the specification may rely on the state of the prior art to help enable the invention, the specification may not rely on the state of prior art to supplement what is critical to the practice of the invention- in this case the quantified levels of control RNA encoded by the gene in the control subjects, no matter which type of control subjects.

Applicant states that the data set forth by Twine et al. only relates to genes which are expressed in peripheral blood mononuclear cells, and the instant claims are drawn to RNA of samples which comprise unfractionated leukocytes. Not a single claim in the instant claim set is so limited. Every independent claim includes any type of blood sample or RNA from blood samples. Claim 50 includes as an option whole blood samples and does not include the inclusion of further steps of isolation, stating that the quantifying is a level of RNA encoded by the DMN gene **in a blood sample**, wherein the blood sample is a whole blood sample. The Twine et al. take a whole blood sample and further process it, which is encompassed by even claim 49. No claim requires that the total RNA from unfractionated leukocytes is tested, as applicant states, and so the arguments are not commensurate in scope with the claims.

Further, there is no evidence on record that the relationship observed by Twine et al. would not be observed in a total blood RNA sample. Even more, it is irrelevant to the point, which is that it is highly unpredictable whether or not the differential expression observed for DMN in OA versus healthy patients can be distinguished from that observed by Twine et al. for

patients having RCC. Applicants state that it cannot be predictably extrapolated that the global differential expression of any given gene observed in PMBC will also be observed in unfractionated cells. This paper is exemplary of the fact that without extensive further experimentation- at the very least without confirmation- one cannot apply the asserted relationship between DMN expression and OA. In fact, one cannot know from the specification what that relationship is, and if one attempted to replicate it, one would not know if they did replicate it since the data given in the specification is incomplete.

Furthermore, it is again noted that the specification itself exemplifies that DMN is not differentially expressed in subjects having a variety of comorbidities with OA. So the relationship is not robust. It is highly unpredictable, then, which additional comorbidities or phenotypes might change the expression of DMN in blood samples.

Applicant disagrees with the contention based on Wu et al. that expression data needs to be interpreted in view of other biological knowledge (page 15). Wu was relied upon for much more than this simple statement. Wu discusses at length many of the factors that make gene expression analysis unpredictable. Applicant's statement that "differential gene expression which is reproducible, and is correlated with the state of health or disease of the individual does not necessarily result directly in the state of the disease of the individual" is attorney argument which is not supported by evidence on the record. Even if the changes are a result of downstream effects of the pathogenic process, they are related to the state of disease in the individual. Applicant points out that certain prostate markers were used as biomarkers without an understanding of their function. The examiner is not trying to require an understanding of DMN in OA or any other disease, nor does Wu suggest that such is necessary. The examiner is looking

to the specification for adequate guidance for making and using an invention in a highly

unpredictable field of endeavor.

Applicant states that the results of Cheung et al. cannot be reliably extrapolated to

primary blood samples since Cheung et al. are using cultured cell lines. However, this is

irrelevant to the point of Cheung et al. which is that among individuals (in this case cell lines)

there is natural variability in gene expression for any particular gene. Attorney arguments are not

sufficient to establish that this biological fact is not the case.

Applicant suggests that extending the findings of the instant application to larger samples

is merely routine. However, in the absence of the critical disclosure of the specification and the

unpredictable nature of the technology, the further experimentation is inventive- applicant has

provided one of skill in the art with an invitation to discover the actual relationship between

DMN expression in the blood and OA.

The instant situation differs tremendously from In re Angstadt, wherein a large number

(forty) examples were provided, only one of which did not work. In In re Angstadt, the court

determined that there was sufficient guidance in an unpredictable art. The court further stated,

however, that "each case must be determined by its own facts." The facts of this case do not

support an enabled use for the claims, for all of the reasons discussed in the rejection. Here, the

situation is quite different because the specification does not provide data or guidance sufficient

to support the claims of any embodiment of the claimed invention, let alone multiple

embodiments.

Conclusion

11.   No claim is allowed.

12.   Applicant's amendment necessitated the new ground(s) of rejection presented in this
Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).
Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE
MONTHS from the mailing date of this action. In the event a first reply is filed within TWO
MONTHS of the mailing date of this final action and the advisory action is not mailed until after
the end of the THREE-MONTH shortened statutory period, then the shortened statutory period
will expire on the date the advisory action is mailed, and any extension fee pursuant to 37
CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,
however, will the statutory period for reply expire later than SIX MONTHS from the date of this
final action.

13.   Any inquiry concerning this communication or earlier communications from the
examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The
examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until
4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's
supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is
assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this
application or proceeding should be directed to the receptionist whose telephone number is
(571)272-0507.

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viewed in the Patent Application Information Retrieval system (PAIR) can now contact the

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9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

February 25, 2008